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The Relative Strength of C-Reactive Protein and Lipid Levels as Determinants of Ischemic Stroke Compared With Coronary Heart Disease in Women

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OBJECTIVES We sought to determine the relative strength of high-sensitivity C-reactive protein (hs-CRP) and lipid levels as markers for future ischemic stroke compared with coronary heart disease (CHD) in women.

BACKGROUND Although hs-CRP and lipid levels are established risk determinants for vascular disease, the relative strength of these biomarkers for ischemic stroke compared with CHD is uncertain.

METHODS Among 15,632 initially healthy women who were followed for a 10-year period, we compared hs-CRP, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), non–high-density lipoprotein cholesterol (non-HDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoproteins A-I and B100, and lipid ratios as determinants of ischemic stroke compared with CHD.

RESULTS After adjustment for age, smoking status, blood pressure, diabetes, and obesity, the hazard ratios (HRs) and 95% confidence intervals (CIs) for the third versus the first tertile for future ischemic stroke compared with CHD were, respectively, 1.91 (95% CI 1.13 to 3.21) and 2.26 (95% CI 1.64 to 3.12) for TC, 1.29 (95% CI 0.83 to 2.02) and 2.09 (95% CI 1.53 to 2.85) for LDL-C, 0.57 (95% CI 0.36 to 0.92) and 0.38 (95% CI 0.27 to 0.52) for HDL-C, 1.72 (95% CI 1.03 to 2.86) and 2.93 (95% CI 2.04 to 4.21) for non–HDL-C, and 2.76 (95% CI 1.51 to 5.05) and 1.66 (95% CI 1.17 to 2.34) for hs-CRP. Of the lipid ratios, that of TC to HDL-C had the largest HR for both future ischemic stroke and CHD (HR 1.95 [95% CI 1.16 to 3.26] and 4.20 [95% CI 2.79 to 6.32], respectively).

CONCLUSIONS In this large prospective cohort of initially healthy women, lipid levels are significant risk determinants for ischemic stroke, but with a magnitude of effect smaller than that observed for CHD. High-sensitiviy CRP associates more closely with ischemic stroke than with CHD. Concomitant evaluation of lipid levels and hs-CRP may improve risk assessment for stroke as well as CHD. (The Women's Health Study; http://www.clinicaltrials.gov/ct/show/NCT00000479/; NCT00000479) (J Am Coll Cardiol 2006;48:2235–42) © 2006 by the American College of Cardiology Foundation

Although hyperlipidemia and inflammation play major roles in atherothrombosis, there has been controversy regarding the relative contribution of these processes to ischemic stroke compared with coronary heart disease (CHD). For example, although both lipid levels and high-sensitivity C-reactive protein (hs-CRP) predict CHD (1–8), several studies have not found lipid levels to predict incident stroke (9–15). In contrast, some earlier studies of hs-CRP and other inflammatory biomarkers have suggested that these markers are closely associated with future stroke, although data are somewhat limited in women (2,16–19). Although methodologic issues, such as considering only fatal stroke (12), combining hemorrhagic and ischemic stroke as a single end point (11), or being restricted to somewhat limited sample sizes (9,10), may have contributed to the lack of a relationship between cholesterol and stroke described by many investigators, it is also possible that inflammation and hyperlipidemia contribute differentially to clinical events in the cerebral and coronary vascular beds.

To address these issues, we analyzed a full lipid panel and hs-CRP in a large-scale cohort of women with the specific aim of evaluating the magnitude of risk for each biomarker for ischemic stroke compared with CHD.

METHODS

The Women's Health Study (WHS) is a randomized double-blind placebo-controlled 2 × 2 factorial design trial of aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer among initially healthy women aged 45 years or older. Participants were enrolled

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Abbreviations and Acronyms

ARIC	= Atherosclerosis Risk in Communities
CHD	= coronary heart disease
CI	= confidence interval
HDL-C	= high-density lipoprotein cholesterol
HR	= hazard ratio
hs-CRP	= high-sensitivity C-reactive protein
LDL-C	= low-density lipoprotein cholesterol
LR	= likelihood ratio
TC	= total cholesterol
WHS	= Women's Health Study

between November 1992 and July 1995 and were followed prospectively for all cardiovascular events, including nonfatal myocardial infarction, nonfatal stroke, coronary revascularization procedures, and cardiovascular-related death. All participants in the WHS provided written informed consent, and the study protocol was approved by the institutional review board of the Brigham and Women's Hospital (Boston, Massachusetts).

The methods of end point validation have been described elsewhere in detail (20). Briefly, an end points committee composed of physicians reviewed the medical records of all women who were reported to have suffered a cardiovascular event. Coronary heart disease was defined as a composite of confirmed fatal or nonfatal myocardial infarction, death from coronary artery disease, and coronary revascularization. A myocardial infarction was confirmed if symptoms met World Health Organization criteria and it was accompanied by diagnostic electrocardiographic changes or abnormal elevations in serum cardiac enzymes. Stroke was defined as a new focal neurologic deficit of sudden onset and vascular origin that persisted for more than 24 h. Clinical information and radiographic brain scans were used to distinguish hemorrhagic from ischemic strokes. The interobserver agreement in the classification of stroke into hemorrhagic and ischemic subtypes in the WHS has been shown to be excellent (21).

Among WHS participants, 28,345 women provided blood samples that were stored in liquid nitrogen until the time of analysis. These samples underwent lipid analysis and evaluation for hs-CRP in a core laboratory certified by the National Heart, Lung, and Blood Institute/Centers for Disease Control and Prevention Lipid Standardization program. Levels of total cholesterol and high-density lipoprotein cholesterol (HDL-C) were measured enzymatically on a Hitachi 911 autoanalyzer (Roche Diagnostics, Basel, Switzerland), and low-density lipoprotein cholesterol (LDL-C) was determined directly (Genzyme, Cambridge, Massachusetts). Levels of apolipoproteins B100 and A-I were measured by an immunoturbidometric technique on the Hitachi 911 analyzer (22). High-sensivity CRP was measured using a validated immunoturbidometric method (Denka Seiken, Tokyo, Japan) (23). Of the samples received by the core laboratory, 27,748 (98%) underwent successful evaluation for each biomarker. Non–HDL-C was calculated by subtracting HDL-C from total cholesterol (TC).

We restricted our analysis to women who were not using hormone therapy at the time of lipid analysis (n = 15,632), because of guidelines issued by the U.S. Department of Health and Human Services (24) and because hormone therapy is known to alter lipid and inflammatory biomarker levels (25–27).

Statistical analysis. Population distributions were computed for each marker, and Spearman correlation coefficients were used to test for relationships between each of the lipid subfractions and hs-CRP. Baseline levels of each blood parameter were divided into increasing tertiles. We used Cox proportional hazards models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for future CHD and ischemic stroke by comparing the second and third tertiles using the lowest tertile as the reference group. The HRs were adjusted on an a priori basis for age, randomized treatment assignment, Framingham blood pressure category, body mass index (BMI), diabetes, and smoking status. For any study participant who suffered both a CHD event and an ischemic stroke, only the first event was used in this analysis. Tests for trends across tertiles of each biomarker were addressed by entering a single ordinal term based on the median value for that biomarker within each tertile. Data analysis was conducted using SAS statistical software version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

Mean (SD) age at baseline for the 15,632 initially healthy women followed for this portion of the study was 53.5 (7.7) years, and the mean (SD) BMI was 26.3 (5.3) kg/m^2. As previously reported (28), TC, LDL-C, non–HDL-C, and apolipoprotein B100 were all highly correlated with one another (r values ranged from 0.76 to 0.93; all significant to $p < 0.0001$). The levels of HDL-C and apolipoprotein A-I were highly correlated with one another ($r = 0.80$) but only weakly correlated with the other lipid variables. In contrast, the correlation between hs-CRP and the lipid variables was weaker, ranging from $r = -0.33$ ($p < 0.0001$) with HDL-C to $r = 0.15$ ($p < 0.0001$) with LDL-C.

Over the follow-up period of 10 years, 468 subjects suffered a first cardiovascular event (132 ischemic stroke, 336 CHD). As expected, there were significant differences in mean age, mean BMI, history of hypertension, diabetes, and smoking status across the groups of women who did not suffer a cardiovascular event and those who reached either cardiovascular end point (Table 1). The median levels of the lipid values, their ratios, and hs-CRP in each of the 3 groups of women are also shown in Table 1. Women with incident CHD were more likely to have a parental history of myocardial infarction before the age of 60 than women with ischemic stroke and had slightly lower HDL-C and apolipoprotein A-I levels. Perhaps because of these differences in HDL-C and apolipoprotein A-I, lipid ratios were slightly

Table 1. Baseline Clinical Characteristics of the Study Participants

Characteristic	Women Without Incident CHD or Ischemic Stroke (n = 15,164)	Women With Incident Ischemic Stroke (n = 132)	Women With Incident CHD (n = 336)	p Value*
Mean age in yrs (SD)	53.3 (7.5)	61.3 (9.1)	58.9 (8.1)	0.006
Mean body mass index (SD)†	26.2 (5.3)	27.3 (5.7)	28.3 (5.8)	0.09
History of hypertension (%)	23.9	55.3	45.8	0.07
History of diabetes (%)	2.9	18.2	19.9	0.67
Parental history of myocardial infarction before age 60 (%)	12.8	9.8	20.1	0.01
History of high cholesterol (%)	26.4	42.4	48.2	0.26
Smoking status‡				
Former	35.5	33.1	33.6	
Current	11.8	23.9	25.6	0.89
Never	52.6	43.1	40.8	
Median cholesterol, mg/dl (IQR)				
Total cholesterol	205.0 (54.0)	228.5 (55.5)	227.0 (53.5)	0.90
LDL	123.2 (44.7)	139.0 (48.3)	141.2 (42.4)	0.38
HDL	49.3 (17.6)	45.2 (16.4)	41.8 (14.5)	0.03
Non-HDL	154.2 (54.4)	175.3 (52.6)	181.4 (50.1)	0.40
Median apolipoprotein, mg/dl (IQR)				
A-I	140.6 (28.4)	135.7 (30.2)	131.7 (25.9)	0.02
B100	98.9 (37.8)	117.1 (45.6)	122.0 (37.3)	0.24
Median high-sensitivity CRP, mg/l (IQR)	1.48 (2.80)	2.85 (5.60)	3.14 (4.24)	0.40
Median lipid ratios (IQR)				
Total cholesterol to HDL-C	4.12 (1.77)	4.99 (2.29)	5.35 (2.02)	0.03
LDL to HDL cholesterol	2.52 (1.33)	3.06 (1.54)	3.33 (1.45)	0.02
Apolipoprotein B100 to A-I	0.71 (0.32)	0.84 (0.46)	0.91 (0.36)	0.03
Apolipoprotein B100 to HDL-C	2.02 (1.26)	2.59 (1.83)	2.89 (1.52)	0.02

*The p values are for women with incident ischemic stroke versus those with incident CHD are displayed, and represent *t* tests for normally distributed variables, Wilcoxon 2-sample rank sum tests for variables not assumed to be normally distributed, and chi-square tests for categorical variables. †The body mass index is the weight in kilograms divided by the square of the height in meters. ‡Because of rounding, not all percentages total 100. p values for women with incident ischemic stroke versus those without incident CHD or ischemic stroke were all ≤ 0.0002 except BMI (p = 0.03), parental history of myocardial infarction before age 60 (p = 0.32) and apolipoprotein A-I (p = 0.15). The p values for women with incident CHD versus those without incident CHD or ischemic stroke were all ≤0.0005.

BMI = body mass index; CHD = coronary heart disease; CRP = C-reactive protein; HDL-C = high-density lipoprotein-cholesterol; IQR = interquartile range; LDL-C = low-density lipoprotein-cholesterol.

higher among women with incident CHD compared with women with incident stroke.

The fully adjusted HRs for developing future ischemic stroke and coronary heart disease for each of the single lipid variables and hs-CRP are presented in Table 2. After adjustment for age (years), blood pressure (Framingham categories), diabetes, BMI (kg/m^2), current smoking status, and randomized treatment assignment, increasing tertiles of TC, non-HDL-C, HDL-C, and hs-CRP were all associated with future ischemic stroke (p_{trend} = 0.02, 0.03, 0.02, and 0.003, respectively). Specifically, the HR of future stroke for those women in the highest compared with the lowest tertile was 1.91 (95% CI 1.13 to 3.21) for TC, 1.72 (95% CI 1.03 to 2.86) for non–HDL-C, 0.57 (95% CI 0.36 to 0.92) for HDL-C, and 2.76 (95% CI 1.51 to 5.05) for hs-CRP. Although the associations between increasing tertiles of LDL-C and apolipoproteins B100 and A-I were not statistically significant, the estimates of the HRs were in the expected direction (HR = 1.29, 95% CI 0.83 to 2.02 for LDL-C; HR = 1.47, 95% CI 0.88 to 2.44 for apolipoprotein B100; and HR = 0.72, 95% CI 0.47 to 1.11 for apolipoprotein A-I), consistent with the direction of effect for other highly correlated lipid variables. Among the significant risk determinants for future ischemic stroke, the magnitude of association as measured by the likelihood ratio (LR) chi-square was 213.7 for hs-CRP, 208.0 for TC, 207.3 for HDL-C, and 206.1 for non–HDL-C.

The fully adjusted HRs for lipid ratios as determinants of ischemic stroke are summarized in Table 3. The ratios of TC to HDL-C, LDL-C to HDL-C, and apolipoprotein B100 to HDL-C all associated with future ischemic stroke (p_{trend} = 0.004, 0.01, and 0.03, respectively), and the ratio of apolipoprotein B100 to A-I was of borderline significance (p_{trend} = 0.08). Specifically, the HRs of future ischemic stroke for those in the highest compared with the lowest tertile were 1.95 (95% CI 1.16 to 3.26) for the TC to HDL-C ratio, 1.77 (95% CI 1.08 to 2.90) for the LDL-C to HDL-C ratio, 1.42 (95% CI 0.88 to 2.30) for the ratio of apolipoproteins B100 to A-I, and 1.62 (95% CI 0.98 to 2.68) for the apolipoprotein B100 to HDL-C ratio. The ratio of TC to HDL-C had an LR chi-square of 210.1, which was similar to that of many of the single lipid measures but smaller than for hs-CRP (LR chi-square = 213.7).

As anticipated, all of the measured lipid levels and hs-CRP were associated with future CHD (Table 2). After adjustment, the magnitude of association appeared to be greatest for HDL-C, with an HR of CHD for the highest compared with the lowest tertile equal to 0.38 (95% CI 0.27

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Table 2. Adjusted* Hazard Ratios (HRs) of Future Coronary Heart Disease (CHD) and Ischemic Stroke in Initially Healthy Women According to Tertile of Baseline Lipid Levels and High-Sensitivity C-Reactive Protein (CRP)

Biomarker	Tertile 1	Tertile 2	Tertile 3	p_{trend}
Cholesterol				
Total (range, mg/dl)	<191.0	191.0–224.0	>224.0	
Ischemic stroke events	19	43	70	
HR (95% CI)	1.00	1.70 (0.99–2.93)	1.91 (1.13–3.21)	0.02
CHD events	52	103	181	
HR (95% CI)	1.0	1.50 (1.06–2.13)	2.26 (1.64–3.12)	<0.0001
LDL (range, mg/dl)	<109.9	109.9–138.5	>138.5	
Ischemic stroke events	29	36	67	
HR (95% CI)	1.00	0.87 (0.53–1.44)	1.29 (0.83–2.02)	0.15
CHD events	56	102	178	
HR (95% CI)	1.0	1.44 (1.03–2.02)	2.09 (1.53–2.85)	<0.0001
HDL (range, mg/dl)	<44.0	44.0–55.3	>55.3	
Ischemic stroke events	65	37	30	
HR (95% CI)	1.00	0.71 (0.47–1.08)	0.57 (0.36–0.92)	0.02
CHD events	201	79	56	
HR (95% CI)	1.0	0.48 (0.36–0.63)	0.38 (0.27–0.52)	<0.0001
Non-HDL (range, mg/dl)	<138.4	138.4–173.3	>173.3	
Ischemic stroke events	20	40	72	
HR (95% CI)	1.00	1.36 (0.79–2.35)	1.72 (1.03–2.86)	0.03
CHD events	38	96	202	
HR (95% CI)	1.0	1.75 (1.18–2.59)	2.93 (2.04–4.21)	<0.0001
Apolipoprotein				
A-I (range, mg/dl)	<131.9	131.9–150.2	>150.2	
Ischemic stroke events	56	36	40	
HR (95% CI)	1.00	0.59 (0.38–0.91)	0.72 (0.47–1.11)	0.13
CHD events	170	102	64	
HR (95% CI)	1.0	0.62 (0.48–0.80)	0.44 (0.32–0.60)	<0.0001
B100 (range, mg/dl)	<88.9	88.9–113.9	>113.9	
Ischemic stroke events	21	39	72	
HR (95% CI)	1.00	1.18 (0.69–2.02)	1.47 (0.88–2.44)	0.11
CHD events	31	102	203	
HR (95% CI)	1.0	2.23 (1.47–3.37)	3.25 (2.18–4.82)	<0.0001
High-sensitivity CRP (range, mg/l)	<0.86	0.86–2.60	>2.60	
Ischemic stroke events	17	45	70	
HR (95% CI)	1.00	2.02 (1.11–3.69)	2.76 (1.51–5.05)	0.003
CHD events	55	93	188	
HR (95% CI)	1.0	1.17 (0.82–1.66)	1.66 (1.17–2.34)	0.001

*Adjusted for age in years, blood pressure in Framingham categories, body mass index, diabetes, current smoking status, and randomized treatment assignment.
CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

to 0.52; LR chi-square = 435.2), although the highly correlated variables non–HDL-C (HR 2.93, 95% CI 2.04 to 4.21; LR chi-square = 431.1) and apolipoprotein B100 (HR 3.25, 95% CI 2.18 to 4.82; LR chi-square = 429.7) also showed close association with future CHD.

All of the lipid ratios strongly associated with future CHD (Table 3). In contrast to the single lipid measurements, where non-HDL-C and apolipoprotein B100 were more closely associated with CHD than TC, the lipid ratio with the strongest association was that of TC to HDL-C (HR for highest vs. lowest tertile 4.20, 95% CI 2.79 to 6.32; LR chi-square = 457.4). Similarly, the HR for future CHD for the top versus bottom tertile for the ratio of apolipoprotein B100 to HDL-C was 3.98 (95% CI 2.65 to 5.96; LR chi-square = 452.6).

Figures 1 and 2 present the adjusted HRs for each lipid variable, hs-CRP, and the lipid ratios for those in the highest compared with the lowest tertile. The association between each of the lipid variables and ischemic stroke is similar in direction of effect to its association with CHD. Visually, the HRs for future CHD for all of the lipid variables appear to be slightly stronger than the HR of future ischemic stroke for the same lipid, although we performed no formal statistical comparison. In contrast, the HR for future ischemic stroke for those in the highest tertile of hs-CRP appears to be somewhat larger than the HR of future CHD, although the 95% CIs overlap (HR 2.76, 95% CI 1.51 to 5.05 for ischemic stroke vs. HR 1.66, 95% CI 1.17 to 2.34 for CHD) and no formal statistical comparison was made.

To clarify whether this apparent difference in the strength of association between lipid levels and ischemic stroke compared with CHD was due to a high proportion of cardioembolic strokes caused by atrial fibrillation, we repeated our analysis after excluding all patients who reported either prevalent atrial fibrillation at the time of enrollment in the WHS or subsequently developed the dysrrhythmia during the 10 years of follow-up. Of the 132 women who

Table 3. Adjusted* Hazard Ratios (HRs) of Future Coronary Heart Disease (CHD) and Ischemic Stroke in Initially Healthy Women According to Tertile of Various Lipid Ratios at Baseline

Lipid Ratio	Tertile 1	Tertile 2	Tertile 3	p_{trend}
Total cholesterol to HDL-C (range)	<3.61	3.61–4.77	>4.77	
Ischemic stroke events	22	36	74	
HR (95% CI)	1.00	1.22 (0.70–2.11)	1.95 (1.16–3.26)	0.004
CHD events	28	86	222	
HR (95% CI)	1.0	2.05 (1.32–3.17)	4.20 (2.79–6.32)	<0.0001
LDL-C to HDL-C (range)	<2.13	2.13–2.99	>2.99	
Ischemic stroke events	24	36	72	
HR (95% CI)	1.00	1.22 (0.72–2.07)	1.77 (1.08–2.90)	0.01
CHD events	30	95	211	
HR (95% CI)	1.0	2.31 (1.51–3.53)	4.04 (2.71–6.02)	<0.0001
Apo B100 to Apo A-I (range)	<0.61	0.61–0.82	>0.82	
Ischemic stroke events	25	37	70	
HR (95% CI)	1.00	1.00 (0.59–1.68)	1.42 (0.88–2.30)	0.08
CHD events	33	88	215	
HR (95% CI)	1.0	1.74 (1.15–2.62)	3.41 (2.33–4.98)	<0.0001
Apo B100 to HDL-C (range)	<1.66	1.66–2.49	>2.49	
Ischemic stroke events	24	37	71	
HR (95% CI)	1.00	1.13 (0.66–1.93)	1.62 (0.98–2.68)	0.03
CHD events	29	87	220	
HR (95% CI)	1.0	2.00 (1.30–3.07)	3.98 (2.65–5.96)	<0.0001

*Adjusted for age in years, blood pressure in Framingham categories, body mass index, diabetes, current smoking status, and randomized treatment assignment.
CI = confidence interval; HDL-C = high-density lipoprotein-cholesterol; HR = hazard ratio; LDL-C = low-density lipoprotein-cholesterol.

suffered an ischemic stroke as their first cardiovascular event, 5 had reported atrial fibrillation upon admission to the study and 18 developed atrial fibrillation during the course of follow-up, for a total of 109 women with ischemic stroke who had no history of atrial fibrillation. The point estimates for the HRs of future stroke for the third versus first tertile of each of the lipid values, their ratios, and hs-CRP did not change substantially. Specifically, after multivariable adjustment, the HRs of future ischemic stroke for those in the highest compared with the lowest tertile were 1.87 (95% CI 1.08 to 3.24; p_{trend} = 0.03) for TC, 1.30 (95% CI 0.80 to 2.10; p_{trend} = 0.16) for LDL-C, 0.53 (95% CI 0.32 to 0.89; p_{trend} = 0.01) for HDL-C, 1.64 (95% CI 0.95 to 2.82, p_{trend} = 0.05) for non–HDL-C, 0.70 (95% CI 0.44 to 1.12; p_{trend} = 0.12) for apolipoprotein A-I, 1.42 (95% CI 0.82 to 2.46; p_{trend} = 0.17) for apolipoprotein B100 and 2.65 (95% CI 1.39 to 5.08; p_{trend} 0.007) for hs-CRP. Similarly, those estimates did not change for the lipid ratios, with the HRs of future ischemic stroke for the top versus the bottom tertile equal to 2.24 (95% CI 1.26 to 4.00; p_{trend} = 0.002) for the TC to HDL-C ratio, 1.81 (95% CI 1.06 to 3.10; p_{trend} = 0.02) for the LDL-C to HDL-C ratio, 1.46 (95% CI 0.87 to 2.47; p_{trend} = 0.07) for the ratio of apolipoproteins B100 to A-I, and 1.68 (95% CI 0.97 to 2.91; p_{trend} = 0.03) for the ratio of apolipoprotein B100 to HDL-C. Aside from the point estimate of the HR for the top versus bottom tertile of the TC to HDL-C ratio, which changed from 1.95 (95% CI 1.16 to 3.26) to 2.24 (95% CI 1.26 to 4.00), or approximately 15%, no estimate for any of the HRs for extreme tertiles changed by more than 7% after we excluded women with incident or prevalent atrial fibrillation from the analysis.

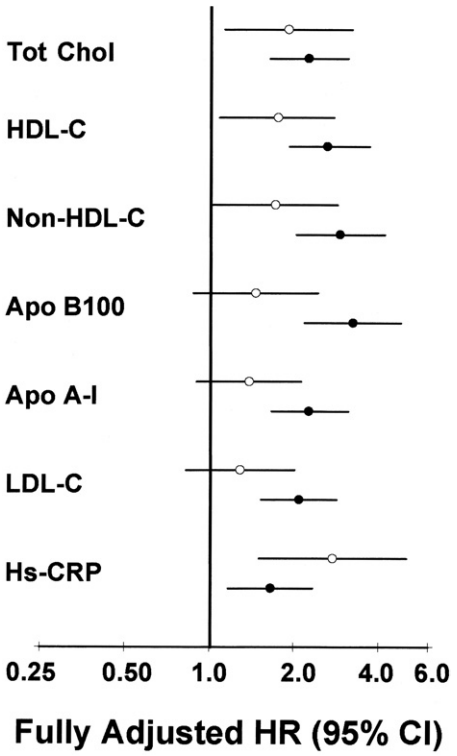

Figure 1. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) for future ischemic stroke **(open circles)** and coronary heart disease **(closed circles)** among those in extreme tertiles of each lipid variable and high-sensitivity C-reactive protein (Hs-CRP). Hazard ratios are adjusted for age (years), blood pressure (Framingham categories), diabetes, current smoking status, body mass index, and randomized treatment assignment. For ease of comparison, we have used the highest tertile as the referent for high-density lipoprotein cholesterol (HDL-C) and apolipoprotein (Apo) A-I. Apo B100 = apolipoprotein B100; LDL-C = low-density lipoprotein-cholesterol; Tot Chol = total cholesterol.

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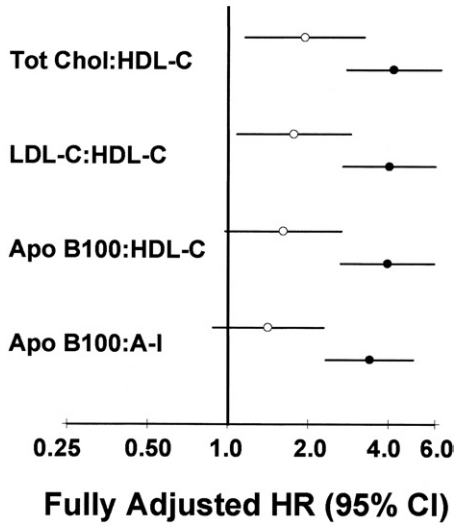

Figure 2. Adjusted hazard ratios and 95% confidence intervals for future ischemic stroke **(open circles)** and coronary heart disease **(closed circles)** among those in extreme tertiles of each lipid ratio. Hazard ratios are adjusted for age (years), blood pressure (Framingham categories), diabetes, current smoking status, body mass index, and randomized treatment assignment. Abbreviations as in Figure 1.

During follow-up only 31 hemorrhagic strokes occurred, and we found no significant linear relationship between hemorrhagic stroke and any of the lipid variables or hs-CRP, using both minimally adjusted (for age and randomized treatment assignment) and fully adjusted proportional hazards models.

Finally, because there is evidence in the literature that exercise (29) and alcohol consumption (30) may be related to stroke risk, and both are known to be related to cholesterol (and in particular HDL-C) levels (31,32), we constructed a Cox model which included exercise (exercise less than 1 time per week, 1 to 3 times per week, and at least 4 times per week) and alcohol consumption (less than 3 drinks per month, 1 to 6 drinks per week, and at least 1 drink per day) in addition to the other variables included in our fully adjusted model. None of the HRs for extreme tertiles of any of the lipid values or hs-CRP changed by more than 5% with the addition of alcohol and exercise to the previously constructed model.

DISCUSSION

In this prospective cohort of initially healthy women, we directly compared standard lipid measures, apolipoproteins B100 and A-I, and hs-CRP as risk determinants for future ischemic stroke compared with CHD. Overall, we found that lipid levels are significantly associated with a risk of future ischemic stroke in a direction similar to that of CHD. However, for all lipid measures, the magnitude of effect appeared smaller for future ischemic stroke than for CHD. Although hs-CRP was a significant predictor of both clinical events, the magnitude of effect, if anything, was somewhat greater for ischemic stroke than for CHD. We could demonstrate no linear relationship between future hemorrhagic stroke and lipid or hs-CRP levels. No substantive differences were observed after exclusion of those with prevalent or incident atrial fibrillation.

We believe these data are clinically relevant for several reasons. First, a clear link between lipids and future stroke has not been established. In our population of initially healthy U.S. women, non–HDL-C and HDL-C were associated with future ischemic stroke risk in a way that was clearly dose-dependent, whereas TC was also associated with future ischemic stroke in a somewhat weaker dose-dependent manner. There was a trend toward an increased risk of ischemic stroke with increasing tertiles of apolipoproteins B100 and A-I and LDL-C, although the trend was not significant. All the lipid ratios except that of apolipoproteins B100 to A-I showed a consistently increasing risk of stroke with increasing levels of the ratio.

As anticipated, lipid levels were all clearly associated with the risks of incident CHD. In all cases but 1 (the ratio of apolipoproteins B100 to A-I), the direction and magnitude of the association between the measured lipid variables and the end points of ischemic stroke and CHD were not significantly different. Although ischemic stroke represents a heterogenous disorder (33), these data provide evidence that in this population hyperlipidemia confers a risk of both ischemic heart disease and ischemic cerebrovascular disease.

Previous literature has noted the lack of association between lipids and ischemic stroke. Some studies have been unable to differentiate between hemorrhagic and ischemic stroke, and have suggested that cholesterol's positive association with ischemic stroke may be concealed by a negative relationship with hemorrhagic stroke (11). Although a relationship between lipids and ischemic and hemorrhagic stroke was suggested by evidence from MRFIT (Multiple Risk Factor Intervention Trial) (34), we could not demonstrate a linear relationship between the risk of hemorrhagic stroke and lipid levels. We are significantly limited, however, by the number of hemorrhagic strokes (n = 31) in our population. Other early research reports may have been limited by sample size (9,10), by combining fatal and incident ischemic stroke (35), or by examining only fatal stroke (12).

More recently, researchers working on a number of well characterized cohorts, such as the ARIC (Atherosclerosis Risk in Communities) study (14) and the Physician's Health Study (15), have reported similarly negative results. In the ARIC cohort, Shahar et al. (14) reported a total of 305 ischemic strokes, 144 of which were in women. Although they do not report the risk associated with elevated levels of TC, non–HDL-C, or the TC to HDL-C ratio, which were the lipid measures that demonstrated the strongest association with future ischemic stroke in our cohort, the HRs of ischemic stroke among women for the highest versus the lowest quartile of LDL-C (HR 1.33, 95% CI 0.81 to 2.20), apolipoprotein B100 (HR 1.61, 95% CI 0.96 to 2.69), and HDL-C (HR 0.68, 95% CI 0.36 to 1.27) are quite similar to the HRs for extreme tertiles of those lipid measures that

we report here. An alternative explanation is that the population of women included in the WHS has fewer established risk factors for ischemic stroke than that recruited for the ARIC study, so that elevated lipid levels play a more central role in the pathophysiology of ischemic stroke among the WHS women.

Although Bowman et al. (15) were unable to show a relationship between cholesterol levels and ischemic stroke in a nested case-control study of 296 ischemic strokes from the Physician's Health Study, other studies performed exclusively in men have demonstrated a positive association between lipids and ischemic stroke (34–37). Investigators working with a cohort of subjects enrolled in a health maintenance organization found an odds ratio (OR) of ischemic stroke of 1.6 (95% CI 1.3 to 2.0) for the highest versus the lowest quintile of TC and a protective effect of the highest levels of HDL-C (OR 0.8, 95% CI 0.6 to 1.0 for extreme quintiles) (33), results that are consistent with recently published findings from Korea (38). Sacco et al. (39), using an ethnically diverse community-based cohort in New York City, also demonstrated a protective effect of high HDL-C levels on the risk of ischemic stroke.

The association we report between hs-CRP and future ischemic stroke has been demonstrated previously in both men (2) and cohorts composed of men and women (16,17). We were able to confirm that relationship in our population of women and to demonstrate that the relationship between hs-CRP and future ischemic stroke (HR 2.76, 95% CI 1.51 to 5.05; LR chi-square = 213.7) was at least as strong as that of the strongest lipid risk determinant, the ratio of TC to HDL-C (HR 1.95, 95% CI 1.16 to 3.26; LR chi-square = 210.1). Whereas the lipid values were highly correlated with one another, the correlations between hs-CRP and the lipid parameters were weaker (range 0.15 to −0.33) (28). This observation is consistent with the hypothesis that both inflammation and hyperlipidemia contribute to the development of ischemic stroke and is consistent with earlier data that markers of inflammation, such as fibrinogen (18) and the leukocyte count (19), are related to incident stroke.

Another possibility is that whereas most ischemic stroke is the result of atherosclerotic processes, cardioembolic stroke (e.g., thromboembolism from atrial fibrillation) may not be closely associated with hyperlipidemia. Although hs-CRP is a well established marker of the systemic inflammation intrinsic to atherosclerosis in this cohort (5) and others (2,6–8), elevated levels of hs-CRP have also been associated with the presence of chronic and paroxysmal atrial fibrillation (40) and may predict incident atrial fibrillation (41). By capturing subjects who are predisposed to both etiologies of ischemic stroke, hs-CRP may serve as a more potent marker of future ischemic stroke than lipids alone. However, our findings that excluding subjects with atrial fibrillation does not substantially alter the point estimates of the hazard ratios for any of the lipids, their ratios, or hs-CRP does not support this hypothesis.

The reliability of our laboratory assays and the large scale and prospective nature of the present cohort serve to reduce the possibility of laboratory error, bias, or chance as explanations for our findings. We elected to exclude women who were using hormone therapy at the time of lipid analysis. Although doing so may limit the generalizability of our results somewhat, we did so on an a priori basis because of guidelines issued by the U.S. Preventive Task Force (24) and because of evidence in the literature that hormone use alters both lipid levels (25,26) and hs-CRP levels (27) and is associated with socioeconomic status, education, exercise, and other unmeasured confounders of CHD and ischemic stroke events (42,43). Because hormone therapy use is declining (44,45), we believe that our results are applicable to a large segment of the U.S. population. Our study included only middle-aged women participating in a randomized controlled trial who are more likely to be healthy than their peers. We measured lipid and inflammatory biomarkers once, and simple intraindividual variability may have altered circulating lipid levels and caused us to misclassify the exposure. However, the overall relationship between lipids and cardiovascular disease in the present study (28) is similar to that in other studies conducted predominantly in men (4). In addition, statin use was very low at the time of lipid analysis in the WHS (20), and the initiation of statins among women with high lipid levels would tend to bias our results toward the null hypothesis.

Our analysis supports the use of standard lipid measures such as TC, HDL-C, non–HDL-C, the ratio of TC to HDL-C, and hs-CRP in the assessment of risk for ischemic stroke in addition to CHD. Although the risk of CHD for a given level of lipid may be somewhat higher than the risk of ischemic stroke, the risks are quite similar in direction. Inflammation, as measured by hs-CRP, and hyperlipidemia appear to play a key role in the development of cerebrovascular atherosclerosis and ischemic stroke, consistent with their well-known role in the pathophysiology of coronary atherosclerosis and CHD.

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